Application No.: 10/568,486

Attorney Docket No.: 33361-US-PCT

Amendments to the Claims

This listing of claims will replace all prior versions, and listings of claims in the specification:

Listing of Claims

Claims 1 -10. (Cancelled)

Claim 11. (Currently Amended) A compound of formula la or lb

Ar
$$X^{\frac{1}{2}}$$
 N $+$ N

or its pharmaceutically acceptable salts in free or sait form, where

Ar is phenyl optionally substituted by one or more substituents selected from halogen, C₁-C₈-alkyl, cyano or nitro:

$$X^2$$
 is $-C(=0)$, O_{-} , CH_{2-1} -S-, -S(=0)- or -S(=0)₂₋₁

m is 1, 2, 3 or 4:

 R^{1} is hydrogen or C_{1} - C_{8} -alkyl optionally substituted by hydroxy, C_{1} - C_{8} -alkoxy, acyloxy, halogen, carboxy, C_{1} - C_{8} -alkoxycarbonyl, $-N(R^{4})R^{5}$, $-CON(R^{5})R^{7}$ or by a monovalent cyclic organic group having 3 to 15 atoms in the ring system;

Q has the formula

where Ra is C1-Ca-alkylene,

or Q is $-C(R^b)(R^c)$ - where R^b and R^c are independently C_1 - C_8 -alkyl or R^b and R^c together form a C_3 - C_{10} -cycloalkyl;

Y is oxygen or sulfur:

 R^2 is hydrogen, C_1 - C_8 -alkyl or C_3 - C_{10} -cycloalkyl and R^3 is C_7 - C_8 -alkyl substituted by phenyl, phenoxy, acyloxy or naphthyl, or R^3 is C_3 - C_{10} -cycloalkyl optionally having a benzo group fused thereto, a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms, phenyl

or naphthyl, said phenyl, phenoxy or naphthyl groups being optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, acyl, nitro, -SO2NH2, C4-C8-alkyl optionally substituted by C₁-C₈-alkoxy, C₁-C₈-haloalkyl, C₁-C₈-alkoxy, C₁-C₈-haloalkoxy, C₁-C₈alkylthio, -SO₂-C₁-C₈-alkyl, C₁-C₈-alkoxycarbonyl, C₁-C₈-acylamino optionally substituted on the nitrogen atom by C₁-C₈-alkyl, C₁-C₈-alkylamino, aminocarbonyl, C₁-C₈-alkylamino-carbonyl, di(C₁-C₈-alkyl)amino, di(C₁-C₈-alkyl)aminocarbonyl, di(C₁-C₈-alkyl)aminocarbonyl-methoxy, or R2 and R3 together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 to 10 ring atoms of which 1, 2 or 3 are hetero atoms; R4 and R5 are each independently hydrogen or C1-C3-alkyl, or R4 is hydrogen and R5 is hydroxy-C₁-C₈-alkyl, acyl, -SO₂R⁸ or -CON(R⁶)R⁷, or R⁴ and R⁵ together with the nitrogen atom to which they are attached denote a 5-or 6-membered heterocyclic group; R⁶ and R⁷ are each independently hydrogen or C₁-C₃-alkyl, or R⁶ and R⁷ together with the nitrogen atom to which they are attached denote a 5- or 6-membered heterocyclic group; and

R⁸ is C₁-C₈-alkyl, C₁-C₈-haloalkyl, or phenyl optionally substituted by C₁-C₈-alkyl,

Claim 12. (Currently Amended) A compound according to claim 11, which is

 $\langle i \rangle$ a compound of formula la or its pharmaceutically acceptable salts in free or salt form. wherein

Ar is phenyl substituted by halo;

m is 2:

R¹ is C₁-C₈-alkyl optionally substituted by hydroxy or C₁-C₈-alkoxy;

Y is oxygen;

R2 is hydrogen; and

R3 is a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms; or (ii) a compound of formula lb or its pharmaceutically acceptable salts in free or salt form, wherein

Ar is phenyl substituted by halo:

m is 1 or 2;

Q has the formula

where Ra is C1-C8-alkylene,

or Q is -C(Rb)(Rb)- where Rb and Rb are independently C1-Cs-alkyl

or Rb and Rb together form a C3-C30-cycloalkyl;

R2 is hydrogen; and

R3 is a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms.

Claim 13. (Currently Amended) A compound according to claim 11, which is

(i) a compound of formula la <u>or its pharmaceutically acceptable salts in free or sait form,</u> wherein

Ar is phenyl substituted by halo, preferably chloro;

m is 2;

R¹ is C₁-C₄-alkyl optionally substituted by hydroxy or C₁-C₄-alkoxy;

Y is oxygen;

R2 is hydrogen; and

 R^3 is a heterocyclic group having 5, 6 or 7 ring atoms of which one, two, three or four, are hetero atoms selected from nitrogen, oxygen and sulphur, said heterocyclic group being optionally substituted by C_1 - C_4 -alky, C_7 - C_4 -alkoxy or C_5 - C_6 -cycloalkyl; or

(ii) a compound of formula lb or its pharmaceutically acceptable salts in free or salt-form, wherein

Ar is phenyl substituted by halo, preferably chloro;

m is 1 or 2;

Q has the formula

where Ra is C1-C8-alkylene,

or Q is -C(Rb)(Rc)- where Rb and Rc are independently C1-C4-alkyl

or Rb and Rc together form a C3-C6-cycloalkyl;

R2 is hydrogen; and

 \mathbb{R}^3 is a heterocyclic group having 5, 6 or 7 ring atoms of which one, two, three or four, are hetero atoms selected from nitrogen, oxygen and sulphur, said heterocyclic group being optionally substituted by C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl.

Claim 14. (Currently Amended) A compound according to claim 11 or a pharmaceutically acceptable salt thereof that is selected from the group consisting of:

1-{(S)-3-[3-(4-Chloro-benzenesuifinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3,5-dimethoxyphenyl)-urea;

1-{(S)-3-[3-(4-Chioro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-ethyl-[1,3,4]thiadiazol-2)-urea;

- 1-{(S)-3-[3-(4-Chloro-benzenesulfinyi)-azetidin-1-yi]-1-hydroxymethyl-propyi}-3-(5-ethyl-2-methyl-2H-pyrazol-3-yi)-urea;
- 1-{(S)-3-{3-(4-Chloro-benzenesulfinyi)-azetidin-1-yi}-1-hydroxymethyl-propyi}-3-(5-cyclopropyi-2-methyl-2H-pyrazol-3-yi)-urea;
- 1-{(S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl}-1-hydroxymethyl-propyl}-3-(5-ethyl-isoxazol-3-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3-ethyl-isoxazol-5-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3,5-dimethoxyphenyl)-urea;
- 1-{(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-ethyl-isoxazol-3-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3-ethyl-isoxazol-5-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-ethyl-[1,3,4]thiadiazol-2-yi)-urea;
- 1-{(S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro- benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{(S)-3-[3-(4-Chloro- benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3,5-dimethoxy-phenyl)-urea;
- 1-{(S)-3-{3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(5-ethyl-isoxazol-3-yl)-urea; and
- 1-{(S)-3-[3-(4-Chloro-benzene-sulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3-ethyl-isoxazol-5-yl)-urea;

- (+/-)1-{(1R,2R)-2-[3-(4-Chloro-phenoxy)-azetidin-1-yl-methyl]-cyclohexyl}-3-(5-ethyl-[1,3,4]thiadiazol-2-yl}-urea;
- 1-((1R,2R)-2-(3-(4-Chloro-phenoxy)-azetidin-1-yl-methyl]-cyclohexyl)-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{(1R,2R)-2-[3-(4-Chloro-phenoxy)-azetidin-1-yl-methyl]-cyclohexyl}-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1 {(1R,2R)-2-{3-(4-Chloro-phenoxy)-azetidin-1-yl-methyl}-syclohexyl}-3-(5-syclobutyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{(1R,2R)-2-[3-(4-Chloro-phenexy)-azetidin-1-yl-methyl]-cyclohexyl}-3-{2-ethyl-2H-tetrazol-5-vl}-urea:
- 1-{(1R,2R)-2-[3-(4-Chloro-phenoxy)-azetidin-1-yl-methyl]-cyclohexyl}-3-(5-ethyl-isoxazol-3-yl)-urea:
- 1-{(1R,2R)-2-{3-(4-Chloro-phenoxy)-azetidin-1-yl-methyl}-cyclohexyl}-3-(3-ethyl-isoxazel-5-yl)-urea;
- 1-(1-{2-[3-(4-Chloro-phenoxy)-azetidin-1-yl]-ethyl]-cyclobutyl)-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea:
- 1-(1-{2-[3-(4-Chloro-phenoxy)-azetidin-1-yl]-ethyl}-cyclobutyl)-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-(1-{2-(3-(4-Chioro phenoxy)-azetidin-1-yl]-ethyl}-cyclobutyl)-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-(1-{2-[3-(4-Chloro-phenoxy)-azetidin-1-yl]-ethyl}-cyclobutyl)-3-(5-cyclobutyl-2-methyl-2H-pyrazol-3-yl)-urea:
- 1-(1-{2-[3-(4-Chloro phenoxy) azetidin-1-yi] ethyi} cyclobutyi)-3-(2-ethyi-2H tetrazoi-5-yi) uroa;
- 1-(1-{2-{3-(4-Chlore-phenoxy)-azetidin-1-yi}-ethyi}-cyclobutyl) 3-(5-ethyl-isoxazoi-3-yi)-urea;
- 1-(1-{2-[3-(4-Chloro-phenoxy)-azetidin-1-yi] ethyl]-cyclobutyl) 3-(3-ethyl-isoxazol-5-yl)-urea;
- 1-{3-{3-(4-Chloro-phenoxy)-azetidin-1-yl]-1,1-dimethyl-propyl}-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)urea:
- 1-{3-{3-(4-Chioro-phenoxy)-azetidin-1-yl]-1,1-dimethyl-propyl}-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{3-{3-(4-Chloro-phenoxy)-azetidin-1-yi]-1,1-dimethyl-propyl}-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea;
- 1-{3-{3-(4-Chloro-phenoxy)-azetidin-1-yi}-1,1-dimethyl-propyl}-3-(5-cyclobutyl-2-methyl-2H-pyrazol-3-yi)-urea;
- 1-{3-{3-(4-Chloro-phenoxy)-azetidin-1-yl}-1,1-dimethyl-propyl}-3-(2-ethyl-2H-tetrazol-5-yl)-urea;
- 1-{3-{3-(4-Chloro-phenoxy) azetidin 1-yl] 1,1-dimethyl-propyl}-3-(5-ethyl-isoxazol-3-yl)-urea; and
- 1-{3-{3-(4-Chloro-phenoxy)-azetidin-1-yl}-1,1-dimethyl-propyl}-3-(3-ethyl-isoxazol-5-yl)-urea.

Claim 15. (Currently Amended) A pharmaceutical composition comprising a compound according to claim 11 or a pharmaceutically acceptable salt thereof in combination with another drug substance which is selected from an anti-inflammatory, a bronchodilator, an antihistamine or an anti-tussive substance.

Claim 16. (Currently Amended) A pharmaceutical composition comprising as active ingredient a compound according to claim 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Claim 17. (**Currently Amended**) A pharmaceutical composition comprising as active ingredient a compound according to claim 14, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent

Claim 18. (Withdrawn – Currently Amended): A method of treating a condition mediated by CCR-3 in a subject in need of such treatment, which comprises administering to said subject an effective amount of a compound of formula Lor a pharmaceutically acceptable salt thereof as defined in claim 11 in free form or in the form of a pharmaceutically acceptable salt.

Claim 19. (Withdrawn – Currently Amended): A method of treating an inflammatory or obstructive airways disease in a subject in need of such treatment, which comprises administering to said subject an effective amount of a compound of formula Lorgan pharmaceutically acceptable sait thereof as defined in claim 11 in free form or in the form of a pharmaceutically acceptable sait.

Claim 20. (Withdrawn): A process for the preparation of a compound of formula la or lb as claimed in claim 11 which comprises

 (i) (A) for the preparation of compounds of formula la where R² is hydrogen, reacting a compound of formula lla

$$Ar - X^{1} \longrightarrow N + \begin{pmatrix} H & H \\ C & - \end{pmatrix}_{m} C - NH_{2}$$
 IIa

or a protected form thereof, where Ar, X¹, m and R¹ are as defined in claim 11, with a compound of formula III

where Y and R3 are as defined in claim 11; or

(B) for the preparation of compounds of formula la where Y is oxygen, reacting a compound of formula lla where Ar, X¹, m and R¹ are as defined in claim 11, with a compound of formula IV

where R2 and R3 are as defined in claim 11; or

- (C) for the preparation of compounds of formula la where X^1 is $-S(=O)_{Z^-}$, oxidising a compound of formula la in protected form where X^1 is -S- and Ar, m, R^1 , Y, R^2 and R^3 are as defined in claim 11;
- (D) for the preparation of compounds of formula lb, reacting a compound of formula lib

$$Ar - X^{2} \longrightarrow N - \left(\begin{array}{c} H \\ \downarrow \\ H \end{array} \right) = Q - NH_{2} \qquad IIII$$

where Ar, X^2 , m and Q are as defined in claim 11, with a compound of formula IV where R^2 and R^3 are as defined in claim 11;

(E) for the preparation of compounds of formula lb where R^2 is hydrogen, reacting a compound of formula llb where Ar, X^2 , m and Q are as defined in claim 11, with a compound of formula V

where R3 is as defined in claim 11; or

- (F) for the preparation of compounds of formula Ib where X is $-S(=O)_{2^{-}}$, oxidising a compound of formula ib in protected form where X^2 is -S- and Ar, m, Q, R^2 and R^3 are as defined in claim 11; and
- (ii) recovering the product in free or salt form.